Multiple Births and Risk of Epithelial Ovarian Cancer

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Background and Methods: **Prevailing hypotheses about the causes of ovarian carcinogenesis predict that women with a history of multiple births (twins, triplets, etc.) should be at increased risk of epithelial ovarian cancer. However, the scant available evidence suggests that they may actually be at lower risk. To resolve this issue, we pooled data from eight studies involving 2859 parous women with epithelial ovarian cancer (case patients) and 7434 parous women without ovarian cancer (control women). In addition to assessing their history of multiple births (and the sex of the children, where available), we obtained information on age, parity, oral contraceptive use, and other reproductive factors for each woman. Details of tumor histology were available for all case patients. We estimated the relative risks of various histologic types of ovarian cancers associated with multiple births by using multivariable logistic regression analysis, adjusting for matching and confounding variables.** ***Results:*** **Among these parous women, 73 case patients (2.6%) and 257 control women (3.5%) had a history of multiple births. The adjusted summary odds ratio (OR) for developing all types of epithelial ovarian cancer that are associated with multiple births was 0.81 (95% confidence interval [CI] = 0.61–1.08). We found no evidence that risks associated with multiple births differed among women with borderline or invasive tumors and among women with same-sex and opposite-sex offspring from multiple births. The risk reductions appeared specific for nonmucinous tumors (n = 2453; summary adjusted OR = 0.71 [95% CI = 0.52–0.98]); in contrast, associations with mucinous tumors (n = 406) were heterogeneous across studies.** ***Conclusions:*** **Parous women with nonmucinous ovarian cancer are no more likely to have a history of multiple births than other parous women, counter to the predictions of current hypotheses for causes of ovarian cancer. [J Natl Cancer Inst 2000;92:1172–7]**

Increasing epidemiologic and experimental evidence indicates that ovarian carcinogenesis is primarily driven by factors associated with reproduction and ovulation *(1,2)*. At least two hypotheses have arisen to explain the causal pathway to ovarian cancer. The "incessant ovulation" hypothesis *(3)* proposes that the chronically repeated cycle of trauma and repair to the ovarian epithelium provides an opportunity for cellular mutation and subsequent neoplasia. The "gonadotropin" hypothesis *(4)* asserts that high levels of gonadotropins cause increased estrogen production by ovarian stromal tissue, which, in turn, promotes epithelial proliferation and malignant transformation.

Most findings from epidemiologic studies are in accordance with both hypotheses; however, several observations remain unexplained. In particular, women with a history of multiple births (i.e., twins, triplets, etc.) have higher levels of gonadotropins during their fertile years *(5,6)*, have a higher incidence of double ovulation per menstrual cycle *(7,8)*, and, thus, would be predicted to be at increased risk of epithelial ovarian cancer if either hypothesis is true. The few available data suggest that mothers of twins are not at higher risk *(9)* and may actually be at substantially lower risk of epithelial ovarian cancer than mothers of singletons (children born one at a time) *(10–12)*. These few isolated reports are far from conclusive evidence of a beneficial effect because the risk estimates have not controlled other factors known to powerfully influence risk of ovarian cancer (such as duration of oral contraceptive use) or have been statistically underpowered to test the association. We have, therefore, pooled the data from eight large case–control studies to explore the association between the risk of the various histologic types of ovarian cancer among women with a history of multiple births.

Subjects and Methods

Data Ascertainment

Data on individual subjects were ascertained from six U.S. case–control studies *(13–18)* that had collected data relating to multiple births and risk of epithelial ovarian cancer but had not published risk estimates for this exposure. Data were also obtained from two case–control studies conducted in Canada *(19)* and in Australia *(12)*; only the latter had published a risk estimate for ovarian cancer associated with a history of twinning. The chief investigators of seven other case–control studies were also approached; however, these studies could not be included for the following reasons: Multiple birth data were not collected or were incompletely collected [three studies *(20–22)*], multiple birth data were no longer available [three studies *(23–25)*], and individual subject data were unable to be retrieved for multiple birth history [one study *(26)*]. All subject data submitted for the pooled analysis were anonymous.

The characteristics of the eight contributing studies are presented in Table 1; specific descriptions of study methodologies are provided in the original publications. The combined dataset included 12 674 women, of whom 2345 (18.5%) reported having no full-term pregnancies. Because the aim was to determine whether a woman's risk of ovarian cancer differed according to whether she had delivered multiple or singleton children, we excluded nulliparous women from all analyses, as well as 35 women with incomplete reproductive histories. The final dataset, therefore, included 10 293 women (2859 case patients with ovarian cancer and 7434 control women without ovarian cancer) who reported at least one full-term pregnancy and for whom details of all pregnancies were complete.

Exposure Information and Data Quality

From each case–control study, data were requested on the occurrence of multiple births for every woman as well as potential confounding factors, including age, number of full-term pregnancies (stillbirths and live births), durations of oral contraceptive use and breast-feeding, family history of breast or ovarian cancer, and history of hysterectomy or tubal ligation. Details of tumor histology were sought for case patients, and analyses were restricted to ovarian cancers of the epithelial type (including both borderline and frankly invasive tumors). All data were checked for internal consistency; where necessary, corrections or clarifications were requested from the original investigators.

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See "Notes" following "References."

Table 1. Characteristics of eight case–control studies of epithelial ovarian cancer

Study (reference No.)	Region	Period of case patient selection	Origin of case patients	Origin of control women	No. of eligible case patients*	No. of control women	Age range of case patients, y	Matching	Confounding variables†
Nasca et al. *(13)*	New York	1977–1980	Cancer registry	Drivers' license records	303‡	806	20–79	Individual matching exact age, county	OC, PREG, HYST§, BF
Hartge et al. *(14)*	Washington, DC	1978–1981	Hospitals	Hospitals	296	343	20–79	Individual matching hospital, age, race	OC, PREG, HYST, TUB, BF
The Cancer and Steroid Hormone Study (CASH) *(15)*	Eight U.S. locations	1980–1982	SEER‖ registers	Random-digit dialing	447¶	3868	20–54	Frequency matching age, location	OC, PREG, HYST, TUB, FAMHIST
Chen et al. *(16)*	Washington state	1986–1988	SEER‖ register	Random-digit dialing	322	430	20–79	Frequency matching age	OC, PREG, HYST, TUB
Risch et al. *(19)*	Ontario, Canada	1989–1992	Cancer registry	Population register	450	564	35–79	Frequency matching age	OC, PREG, HYST, TUB, BF, FAMHIST
Purdie et al. *(12)*	Australia	1990–1993	Treatment centers	Population register	770#	855	18–79	Frequency matching age, urban/rural	OC, PREG, HYST, TUB, BF, FAMHIST
Cramer et al. *(17)*	Massachusetts and New Hampshire	1992–1997	Treatment centers	Random-digit dialing and town lists	563	523	17–75	Individual matching age, residence	OC, PREG, HYST, TUB, BF, FAMHIST
Ness et al. *(18)*	Philadelphia	1993–1998	Hospitals	Random-digit dialing	767	1367	20–69	Frequency matching age, residence	OC, PREG, HYST, TUB, BF, FAMHIST

*Eligible case patients were defined as those with histologically proven epithelial ovarian cancer.

†Information was requested for duration of oral contraceptive use (OC), number of full-term pregnancies (PREG), duration of breast-feeding per pregnancy (BF), history of hysterectomy (HYST), history of tubal ligation (TUB), and history of breast or ovarian cancer in mother or sister (FAMHIST).

‡The dataset from Nasca et al. *(13)* excludes 17 case patients with unknown histology and 83 case patients with nonepithelial ovarian tumors.

§Hysterectomy until time of menopause only.

‖SEER = Surveillance, Epidemiology, and End Results. SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

¶The CASH dataset *(15)* excludes 40 case patients and 370 control women from New Mexico and Utah, for whom fewer variables were collected, and excludes 39 additional case patients with unknown, benign, or secondary ovarian disease.

#The dataset of Purdie et al. *(12)* excludes 22 case patients with peritoneal ovarian tumors.

We defined women as having a history of multiple births if they reported any full-term pregnancies resulting in the birth of more than one infant. In seven of the eight studies, multiple births were identified at the time of interview by specific questioning about the outcome of each pregnancy. For the remaining study *(13)*, multiple births were identified at the time of data processing by an algorithm that assessed all pregnancy events in each woman's reproductive history for similar event dates; possible matches were then individually checked.

Statistical Analyses

The relative risk of ovarian cancer associated with multiple birth was estimated by the odds ratio (OR) and 95% confidence interval (CI). Risk estimates were calculated for all epithelial ovarian cancers in the first instance and then separately for nonmucinous (serous, clear cell, endometrioid, Brenner, and other epithelial types) and mucinous ovarian tumors because there is increasing evidence to support the hypothesis that these types of ovarian cancer are etiologically distinct *(27,28)*. Crude ORs were calculated for each study, and a pooled OR was derived by the method of Mantel–Haenszel *(29)*.

We then undertook multivariable logistic regression analyses to control for the potentially confounding effects of other factors. Because each study collected information on a different set of confounding factors (Table 1), we used two approaches to calculate adjusted risk estimates. First, we calculated partially adjusted risk estimates for multiple birth by adjusting only for the set of potential confounders that was common to all of the studies (i.e., age, duration of oral contraceptive use, number of full-term pregnancies, and hysterectomy). Second, we calculated fully adjusted risk estimates in a model that included terms for all of the common variables (as above), as well as terms for the remaining potential confounders of interest (i.e., average duration of breast-feeding per pregnancy, history of tubal ligation, and history of breast or ovarian cancer in a mother or a sister). Because four studies *(13–16)* did not gather information for one or more of these three additional variables (Table 1), a separate category, named "not collected," was created to accommodate subjects from those studies. In practice, when we restricted the analysis to those studies with the full set of confounding variables, we found very little difference between the partially and fully adjusted risk estimates for multiple birth. We, therefore, considered that these additional variables were not substantive confounding variables and the assignment of some subjects to a "not collected" category was unlikely to introduce bias *(30)*. We have presented only the fully adjusted estimates in the tables. We excluded from the analysis all subjects for whom exposure information was missing (as opposed to not collected). Continuous terms for age (in years) and age-squared (to adjust for residual nonlinear effects of age) and indicator variables for study were included in each regression model. We used the Breslow–Day statistic *(31)* to assess homogeneity of the ORs in the stratified analyses. In the regression analyses, an interaction term, study × multiple birth, was added to a simpler model without this term, and the change in the likelihood ratio statistic was used to assess homogeneity. Heterogeneity was assessed at the $\alpha = .10$ statistical significance level. All P values given are from two-sided tests, and all analyses were performed in SAS version 6.12 *(32)*.

Results

We first estimated the relative risks for all types of epithelial ovarian cancer, regardless of histologic type (n = 2859). Pooling data from all eight studies for parous women, we found that women with ovarian cancer (73 case patients; 2.6%) were less likely to have a history of multiple births than women without ovarian cancer (257 control women; 3.5%)

(Mantel–Haenszel OR = 0.77; 95% CI = 0.59–1.01). Adjustment for maternal age, study, number of full-term pregnancies, duration of oral contraceptive use and breast-feeding, history of hysterectomy or tubal ligation, and history of breast or ovarian cancer in a mother or a sister made little difference to this estimate (Table 2). There was no formal statistical evidence of heterogeneity of the ORs, although it was clear that the point estimate for one study *(13)* was considerably higher than the point estimates of the other seven studies (Table 2). The "outlying" study differed from the remainder in the sampling frame for control women and the way in which multiple births were identified. Because we could not exclude the possibility of bias arising from these methodologic differences, the summary estimates were recalculated after this dataset was excluded (Mantel–Haenszel OR = 0.71 [95% CI = 0.53–0.95]; fully adjusted OR = 0.74 [95% CI = 0.55–1.01]).

Women with nonmucinous ovarian tumors (n = 2453) were less likely to have a history of multiple births than control women in seven of the eight studies (Table 2), and this was reflected in the summary Mantel–Haenszel OR (OR = 0.67; 95% CI = 0.49–0.91). Overall, the effect of statistical adjustment for other confounding factors was negligible (fully adjusted pooled OR = 0.71; 95% CI = 0.52–0.98). Again, we recalculated the summary OR after excluding the outlying study, but we observed little change from the earlier estimate (fully adjusted OR = 0.68; 95% CI = 0.49–0.94).

No consistent pattern of association was observed among the smaller number of women with mucinous ovarian tumors (n = 406). The impression of heterogeneity of the ORs for the crude and the adjusted models was supported by statistical evaluation. Summary ORs were calculated (Table 2); however, because of the heterogeneity, we view these estimates with caution.

We found no evidence that risks associated with multiple births differed among women with invasive (n = 2333) or borderline (n = 526) tumors (OR for invasive tumors = 0.84 [95% CI = 0.62–1.15]; OR for borderline tumors = 0.72 [95% CI = 0.40–1.32]). Information on the sex combination of multiple births was available for 141 women (47 opposite-sex sets and 94 same-sex sets) from five studies *(4,12–14,18)*. The adjusted

Table 2. Odds ratio of epithelial ovarian cancer (crude and fully adjusted) among parous women associated with multiple births, analyzed according to histologic type and stratified by study*

Study (reference No.)	Women, No. multiple/ No. no multiple births	Crude OR (95% CI)	Fully adjusted OR† (95% CI)
		Control women	
Nasca et al. *(13)*	15/669		
Hartge et al. *(14)*	10/249		
CASH *(15)*	128/3184		
Chen et al. *(16)*	11/333		
Risch et al. *(19)*	19/482		
Purdie et al. *(12)*	25/700		
Cramer et al. *(17)*	16/401		
Ness et al. *(18)*	33/1159		
Pooled estimate			
Homogeneity‡			
		All women with epithelial ovarian cancers	
Nasca et al. *(13)*	8/208	1.72 (0.72–4.10)	1.79 (0.72–4.44)
Hartge et al. *(14)*	6/201	0.74 (0.27–2.08)	0.91 (0.31–2.67)
CASH *(15)*	12/325	0.92 (0.50–1.68)	1.12 (0.60–2.08)
Chen et al. *(16)*	7/235	0.90 (0.35–2.36)	0.64 (0.24–1.73)
Risch et al. *(19)*	8/337	0.60 (0.26–1.39)	0.71 (0.30–1.68)
Purdie et al. *(12)*	12/591	0.57 (0.28–1.14)	0.60 (0.29–1.22)
Cramer et al. *(17)*	12/366	0.82 (0.38–1.76)	0.77 (0.35–1.69)
Ness et al. *(18)*	8/523	0.54 (0.25–1.17)	0.59 (0.26–1.30)
Pooled estimate		0.77 (0.59–1.01)	0.81 (0.61–1.08)
Homogeneity‡		$\chi^2 = 5.77$ ($P = .57$)	$\chi^2 = 6.42$ ($P = .49$)
		Women with nonmucinous ovarian cancers only	
Nasca et al. *(13)*	5/178	1.25 (0.45–3.50)	1.39 (0.48–4.03)
Hartge et al. *(14)*	6/187	0.80 (0.29–2.24)	0.95 (0.32–2.81)
CASH *(15)*	7/277	0.63 (0.29–1.36)	0.77 (0.35–1.70)
Chen et al. *(16)*	5/211	0.72 (0.25–2.09)	0.51 (0.17–1.55)
Risch et al. *(19)*	4/274	0.37 (0.13–1.10)	0.44 (0.14–1.36)
Purdie et al. *(12)*	11/504	0.61 (0.30–1.25)	0.66 (0.32–1.39)
Cramer et al. *(17)*	10/317	0.79 (0.35–1.77)	0.73 (0.32–1.68)
Ness et al. *(18)*	8/449	0.63 (0.29–1.37)	0.69 (0.31–1.54)
Pooled estimate		0.67 (0.49–0.91)	0.71 (0.52–0.98)
Homogeneity‡		$\chi^2 = 3.06$ ($P = .88$)	$\chi^2 = 3.31$ ($P = .85$)
		Women with mucinous ovarian cancers only	
Nasca et al. *(13)*	3/30	4.46 (1.23–16.24)	3.27 (0.79–13.55)
Hartge et al. *(14)*	0/14	0	0
CASH *(15)*	5/48	2.59 (1.01–6.62)	2.99 (1.15–7.77)
Chen et al. *(16)*	2/24	2.52 (0.53–12.04)	2.35 (0.46–11.97)
Risch et al. *(19)*	4/63	1.61 (0.53–4.89)	1.71 (0.54–5.40)
Purdie et al. *(12)*	1/87	0.32 (0.04–2.41)	0.28 (0.04–2.15)
Cramer et al. *(17)*	2/49	1.02 (0.23–4.58)	1.03 (0.22–4.81)
Ness et al. *(18)*	0/74	0	0
Pooled estimate		1.27 (0.77–2.10)	1.28 (0.76–2.15)
Homogeneity‡		$\chi^2 = 12.92$ ($P = .07$)	$\chi^2 = 15.31$ ($P = .03$)

*OR = odds ratio; CI = confidence interval; CASH = The Cancer and Steroid Hormone Study.

†Unconditional logistic regression analysis adjusted for exact age, age-squared, number of full-term pregnancies, duration of oral contraceptive use (in months), hysterectomy, average duration of breast-feeding per pregnancy, history of breast or ovarian cancer in mother or sister, and tubal ligation. Not all studies had complete information for all confounding variables (*see* Table 1 for list of confounder availability).

‡Homogeneity was assessed by testing the Breslow–Day statistic (for the crude ORs in stratified analyses) or the likelihood ratio statistic (for the interaction term in the regression analyses) against the χ^2 distribution with (n – 1) degrees of freedom. All *P* values are from two-sided tests.

OR for epithelial ovarian cancer (of all histologic types) among women with opposite-sex offspring from multiple births was 0.76 (95% CI = 0.39–1.45), and the adjusted OR among women with same-sex offspring was 0.80 (95% CI = 0.51–1.25). Restricting the analysis to include only those women with nonmucinous ovarian cancers, we observed ORs of 0.73 (95% CI = 0.37–1.47) and 0.79 (95% CI = 0.49–1.27) for opposite-sex and same-sex multiple birth sets, respectively.

Finally, we grouped women according to their total number of full-term pregnancies. We found similarly reduced ORs for nonmucinous epithelial ovarian cancers in each group, although none of the estimates was statistically significantly reduced (Table 3). We observed no such consistency of effect with mucinous ovarian cancers.

Discussion

Several models have been proposed to explain the etiology of ovarian cancer; principal among these have been the incessant ovulation *(3)* and gonadotropin *(4)* hypotheses. Although both of these models account for most epidemiologic observations in the occurrence of this disease, both models predict that women with a history of multiple births should be at increased risk for epithelial ovarian cancer. For example, double ovulations are more frequent among mothers of naturally occurring dizygotic twins than among mothers of singletons *(7,8)*. If so, then under the incessant ovulation hypothesis, such women will cumulatively suffer more epithelial trauma and, therefore, be at higher risk of ovarian cancer than age-matched, equiparous mothers of singletons. The gonadotropin hypothesis postulates that factors that predispose to higher levels of gonadotropins will increase the risk of ovarian cancer *(4)*. Because most published studies *(5,6,33)*, but not all *(8)*, have reported that mothers of twins have higher serum levels of gonadotropins than mothers of singletons, this hypothesis also predicts that such women ought to be at higher risk of ovarian cancer. Our finding that women with epithelial ovarian cancer were less likely to have a history of multiple births is, therefore, clearly at odds with both of these hypotheses.

Several features of our investigation suggest that our observations reflect a real reduction in risk and are not the result of artifact. The magnitudes of the risk estimates were remarkably consistent across the individual studies, and the effects persisted after adjustment was made for reproductive and other factors known to powerfully influence the risk of both ovarian cancer and multiple births. One factor that was not controlled in our analyses was the use of fertility treatments, principally because this information was not collected in most of the studies. The use of fertility treatments is potentially an important source of confounding because multiple births are more common among women who have taken fertility treatments and because these drugs have been associated with increased risks of ovarian cancer *(34)*. It might, therefore, be argued that any association between multiple births and ovarian cancer is spurious and simply due to confounding introduced by differing levels of exposure to fertility treatments. If so, then one would expect women with a history of multiple births to have higher levels of exposure to these medications than other parous women and, therefore, to be at increased risk of epithelial ovarian cancer. We observed the opposite association in seven of the eight studies and conclude that, if confounding of this type did occur in these datasets, then the true effect of multiple births may be even more protective than we have estimated. Even so, the possibility of confounding by fertility drugs is remote because this analysis was restricted solely to parous women who had mostly completed their families before widespread availability of these treatments.

We cannot exclude a role for selection or information biases in contributing to these pooled results; however, overall, we consider the likelihood to be small. For example, it is possible that a woman 's decision to participate in a study may have been influenced by whether or not she had a history of multiple births, but the fact that similar effects were observed regardless of the number of pregnancies argues otherwise. We have no reason to suspect that women with ovarian cancer systematically misclassified or underreported their multiple pregnancies (or the converse for control women). It is similarly unlikely that, within each study, interviewers systematically elicited multiple birth information differently for case patients and control women because this was not a primary hypothesis for any of the studies. The only study that did not specifically record multiple birth data at the time of interview was the only study

Table 3. Odds ratio of epithelial ovarian cancer (by histologic type) associated with multiple births, stratified by number of full-term pregnancies*

No. of full-term pregnancies	Control women, No. multiple/No. no multiple births	All women with epithelial ovarian cancers		Women with nonmucinous ovarian cancers only		Women with mucinous ovarian cancers only	
		No. multiple/No. no multiple births	OR (95% CI)†	No. multiple/No. no multiple births	OR (95% CI)	No. multiple/No. no multiple births	OR (95% CI)
1	22/1021	9/557	0.76 (0.32–1.82)	7/469	0.66 (0.26–1.70)	2/88	1.21 (0.25–5.81)
2	51/2420	19/1004	1.03 (0.57–1.87)	14/874	0.89 (0.46–1.73)	5/130	1.92 (0.72–5.09)
3	67/1815	16/674	0.64 (0.35–1.14)	15/590	0.66 (0.36–1.21)	1/84	0.35 (0.05–2.64)
4	51/1036	11/317	0.64 (0.31–1.31)	10/265	0.70 (0.33–1.49)	1/52	0.34 (0.46–2.61)
≥5	66/884	18/234	1.04 (0.56–1.92)	10/199	0.62 (0.29–1.32)	8/35	2.92 (1.20–7.10)
Homogeneity‡			$\chi^2 = 2.39$ ($P = .66$)		$\chi^2 = 0.69$ ($P = .95$)		$\chi^2 = 9.22$ ($P = .06$)

*OR = odds ratio; CI = confidence interval.

†Unconditional logistic regression analysis, adjusting for exact age, age-squared, study, duration of oral contraceptive use (in months), hysterectomy, duration of breast-feeding, history of breast or ovarian cancer in mother or sister, and tubal ligation. Not all studies had complete information for all confounding variables (*see* Table 1 for list of confounder availability).

‡Homogeneity was assessed by testing the liklihood ratio statistic (for the interaction term of number of full-term pregnancies and multiple births) against the χ^2 distribution with (n − 1) degrees of freedom. All *P* values are from two-sided tests.

to generate a risk estimate greater than 1. To analyze this study, we derived a multiple-birth variable by using a computer algorithm based on shared-event dates in the obstetric history. Because the prevalence of multiple births among control women in that study (2.2%) was noticeably lower than that in the other studies (3.6%), we suspect that this method may not have identified all women with a history of multiple births. Moreover, control women in that study were sampled from drivers' license files and, thus, may differ from the population in which the case patients arose in terms of social class, reproductive history, and other ways likely to influence risk. Consequently, despite the lack of formal evidence for heterogeneity, we took the precaution of repeating certain analyses after excluding those data.

Our findings of a reduced risk of epithelial ovarian cancer associated with multiple births are in general agreement with record linkage studies from Denmark *(11)* and Sweden *(10)*, which reported lower risks of ovarian cancer among mothers of twins. Neither of those studies was able to control for important confounding variables, however, and neither conducted separate analyses for nonmucinous and mucinous tumors. Our analysis suggests that the effect of multiple births is specific for nonmucinous tumors and lends support to the hypothesis that ovarian neoplasms are etiologically heterogeneous *(27)*.

Thus, the qualitatively consistent findings observed in case–control studies and record-linkage studies provide strong grounds for rejecting the notion that women with a history of multiple births are at increased risk of ovarian cancer, as predicted by the two prevailing hypotheses. The question arises as to why this should be. From the collected data, we infer that other factors, in addition to either ovulatory trauma or gonadotropin levels, must be operating that influence a woman's risk of ovarian cancer. One suggestion is that the surge in progesterone synthesis during pregnancy confers protection to the ovarian epithelium *(2)*. It has been observed previously *(35)* that the reduction in risk conferred by each full-term pregnancy is greater than the benefit incurred by an equivalent period of amenorrhea alone, consistent with the notion that the hormonal milieu of pregnancy is beneficial in addition to the respite it affords from ovulatory trauma. Because progesterone levels during multiple pregnancies are considerably higher than during singleton pregnancies *(36–38)*, this same mechanism could explain why multiple pregnancies are super-protective over and above the benefits of other full-term pregnancies. We found reduced risks of ovarian cancer, regardless of the sex combination (and by inference, the zygosity) of the multiple births, which suggests that the effect is associated directly with the multiple-birth event and is not related to factors specifically associated with monozygotic or dizygotic twinning.

If progesterone (or some other hormone of pregnancy) does reduce the risk of ovarian cancer, it remains to be determined why the effect is additive and how it is produced. Adami et al. *(39)* have speculated that pregnancy clears the ovary of cells that have previously undergone malignant transformation and that this effect might be mediated by steroid hormones. This hypothesis awaits empirical testing at the cellular level but may explain our epidemiologic findings. Given the rarity of ovarian cancer and multiple births as well as the scarcity of studies that have collected information on both, we would encourage exploration of any other datasets that may further our understanding of the role of multiple births in ovarian cancer.

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